Health Canada Santé Canada

Your health and safety... our priority. *Votre santé et votre sécurité... notre priorité.*

Regulatory Proposal PRO2018-01

Consultation on Proposed Regulatory Changes for Pesticide Products Used on Companion Animals

(publié aussi en français)

21 September 2018

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
hc.pmra.publications-arla.sc@canada.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
hc.pmra.info-arla.sc@canada.ca

Canada

ISSN: 1197-740X (print)
1925-122X (online)

Catalogue number: H113-8/2018-1E (print)
H113-8/2018-1E-PDF (PDF version)

© Her Majesty the Queen in Right of Canada, represented by the Minister of Health Canada, 2018

All rights reserved. No part of this information (publication or product) may be reproduced or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, or stored in a retrieval system, without prior written permission of the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5.

Table of Contents

1.0 Introduction 2
1.1 Product Details and Value 3
2.0 Analysis of Animal Incident Reports 4
2.1 General Results of the Analysis of Animal Incident Reports 5
3.0 Animal Safety Testing Strategies 9
4.0 Other Available Information 10
5.0 Conclusion 11
5.1 Proposed Label Requirement 12
5.2 Proposed Data Requirement 12
6.0 Next Steps 13

1.0 Introduction

Products applied to the skin of cats and dogs for flea and tick control are regulated under the *Pest Control Products Act*. These include sprays, powders, shampoos, impregnated collars, and most notably, spot-on products. An issue related to the high number of reported incidents for dogs and cats treated with spot-on products was first identified as a concern by the Pest Management Regulatory Agency (PMRA) in 2009.[1] As a result, the PMRA published an advisory to inform consumers about the potential risks that may be associated with these products and to remind them to follow label directions. An in-depth review of spot-on incident data was subsequently undertaken in conjunction with the United States Environmental Protection Agency (USEPA). In addition, the PMRA discussed the concerns with the Canadian Veterinary Medical Association. The PMRA also solicited the opinion of small animal veterinarians through a survey in order to gather more information about potential issues related to these products.[2]

As a result of the review of the incidents, the PMRA released the findings in a March 2010 update to the public advisory,[3] and implemented label changes in 2011 under the Regulatory Directive DIR2010-02, "Label Improvements for Spot-on Pesticides Used for Flea and Tick Control on Companion Animals", to address the key concerns. Specifically, the words 'Toxic to cats' and a corresponding pictogram were added to the principal display panel of the label of spot-on products containing permethrin, since the application to cats of products intended for use on dogs containing permethrin resulted in a high number of cases of misuse. Signs of adverse effects in cats included effects such as hyperesthesia, body tremors, muscle fasciculations and convulsions. Additional precautionary label statements were required regarding potential sensitivity of smaller animals as well as prevention of exposure of untreated animals.[4] The USEPA identified the same concerns and took similar action.

Since the 2011 label amendments, a decline in the number of cases of misuse involving cats treated with permethrin spot-on products was observed. Despite this, the overall number of incidents reported for spot-on products continued to increase over time, which prompted the PMRA to initiate an updated and more in-depth review of the incident data. As indicated in the Proposed Re-evaluation Decisions for permethrin (PRVD2017-18) and imidacloprid (PRVD2016-20), the present review represents a broader examination of domestic animal incident data for all registered spot-on products.

The updated review was conducted on all spot-on incident data reported to the PMRA from 2007 up to the end of 2015. The PMRA analyzed 5928 incident reports in dogs and cats involving spot-on products. The majority of these incidents (73%) occurred in Canada (4359). The remaining 27% comprised reported animal incidents involving death in the United States. The

---

1 "Report on Pesticide Incidents for 2008-2009."

2 Turner, V., Chaffey, C. and P. Ferrao. "A survey for small animal veterinarians regarding flea and tick control pesticide products," *Can. Vet. J.*, vol. 52, no. 10, pp. 1080-1082, 2011.

3 "Health Canada Reminds Consumers to Follow Label Directions on Flea and Tick Pest Control Products." Health Canada Advisory. March 17, 2010.

4 "DIR2010-02 Label Improvements for Spot-on Pesticides Used for Flea and Tick Control on Companion Animals." Health Canada, Pest Management Regulatory Agency. September 2, 2010.

PMRA requires this small subset of all American incident reports that occur with similar products to be reported to the PMRA under the *Incident Reporting Regulations*.[5] This subset of American data is used to support the post-market review of pesticides conducted at the PMRA, as well as any new active ingredient proposed for Canadian registration, when applicable. Although not a requirement, a small number of minor or moderate incidents that occurred in the United States were submitted to the PMRA.

Following the analysis, the PMRA received additional information from permethrin spot-on product registrants, as well as consulted with the Canadian Veterinary Medical Association[6] to seek its opinion on the issue and to discuss the impact of possible mitigation measures. This additional information was taken into consideration by the PMRA in developing this regulatory proposal. As per subsection 28(2) of the *Pest Control Products Act*, the proposed amendments are open to public consultation.

The PMRA invites the public to submit written comments up to 45 days from the publication of this regulatory proposal. Please forward all comments to PMRA Publications. (Contact information can be found on the cover page of this document).

1.1 Product Details and Value

Spot-on products are applied to cats to control fleas, and to dogs to control fleas, lice, ticks, and mosquitoes. Fleas cause discomfort to the host animals, and flea bites, irritation, and scratching by the host animal can lead to secondary medical issues such as pruritus, dermatitis, and infection. In addition, dogs and cats can develop allergic hypersensitivity to fleas, and fleas can transmit infection and disease such as tapeworm, *Rickettsia felis* (spotted fever), cat scratch fever, and Bartonellosis. Fleas are also a source of discomfort, irritation, and nuisance to humans. Lice can cause discomfort and irritation to host animals, and can cause hair loss, excessive itching and scratching, and anemia with severe infestations. As with fleas, scratching can lead to secondary medical issues. Ticks can transmit Lyme disease to both dogs and humans, and mosquitoes are a serious nuisance pest and can transmit disease including heartworm to dogs.

Pesticidal active ingredients registered for use in spot-on products for use on dogs and/or cats include (S)-methoprene, pyriproxyfen, d-Phenothrin, permethrin, and imidacloprid. Many products are packaged in ready-to-use tubes of different volumes in order to achieve the appropriate dose for dogs or cats of a specific size (based on labelled weight ranges, also known as 'weight-banding'). Labels also indicate the minimum age of animals to be treated. Pesticide products which can be used as alternatives to spot-on products include sprays, powders, shampoos, and impregnated collars.

Spot-on products have value as they are easy to apply and provide prophylactic and long-lasting (usually about 3 to 4 weeks) pest control following a single application.

---

5 "Pest Control Products Incident Reporting Regulations (SOR2006-260)."

6 "Health Canada consults with CVMA regarding flea and tick spot-on products." Canadian Veterinary Medical Association, January 12, 2018.

2.0 Analysis of Animal Incident Reports

In veterinary pharmacovigilance, a rate of one incident or more per 10 000 units of product sold is used as a trigger for an investigation in some jurisdictions.[7] [8] The PMRA also considered this trigger during the analysis of spot-on incidents. When data for all spot-on products were combined, the overall rate was 1.42 incidents/10 000 units sold, and rates for individual products ranged from less than 1 up to 10 incidents/10 000 units sold (a ready-to-use tube was considered as one unit). The severity of incidents in combination with the volume of incidents reported can also serve as a trigger for investigation, regardless of the incident rate.

It was noted in the Canadian incidents received that 58% of the animals experienced minor effects which resolved rapidly; 35% experienced effects which generally required medical treatment; 5% experienced life-threatening effects; and 2% died. The number of reported incidents where a pet received medical treatment was of concern to the PMRA.

Based on the above-noted concerns, further analysis of the incident reports was conducted in an attempt to explain the reasons for the large volume of incident reports. Since pesticide incident reports reflect a suspected association between the reported effects and exposure to a pesticide product, a weight of evidence approach was taken to determine the relationship between the suspected pesticide exposure and the reported effects (that is, the level of causality) in order to further refine this assessment.

Several factors were considered in the assessment of causality. The reported signs were compared to the effects seen in toxicological studies conducted with the active ingredients and their associated spot-on products and to the effects observed in cats and dogs in the available companion animal safety (CAS) studies. Additionally, comparisons to the available toxicological information on the formulants contained in the spot-on products were made. Repetition of effects within the incident reports was also considered during the causality review.

In 11% of spot-on incidents reported to the PMRA (680 incidents), the product was not used according to label directions. Most of these cases of misuse involved the application to cats of a permethrin-containing product that is registered for use on dogs only. This type of misuse was frequently reported in incidents prior to the publication of DIR2010-02. Since the implementation of DIR2010-02, there has been a decrease in the total number of incidents involving cats treated with a permethrin product. This was despite a marked increase in the overall number of incident reports received for permethrin-containing products suggesting that the outreach and label changes implemented under DIR2010-02 had a positive impact on consumer awareness surrounding the importance of correct product use. For the current analysis, incidents involving product misuse were considered separately in order to investigate potential

---

7 "Guideline on a strategy for triggering pharmacovigilance investigations preceding regulatory actions by EU competent authorities. s.l. : European Medical Agency - Veterinary Medicines and Inspections, 2005," European Medicines Agency 's Committee for Medicinal Products for Veterinary Use (CVMP), 13 April 2005.

8 "What Happens Next - Assessing an adverse experience." Australian Government, Australian Pesticides and Veterinary Medicines Authority. September 26, 2017.

regulatory action for cases in which the product was used according to label directions. A small number of incidents (2%) involving indirect exposure to the product applied to another animal and were also excluded from further analysis.

2.1 General Results of the Analysis of Animal Incident Reports

Causality Assessment

Animals were directly exposed to a spot-on product that was used according to label directions in 87% of all incidents. These 5164 incidents were assessed further for causality. Of these, 76% were considered to be causally-related to product use and not to other factors; 54% were determined to have a causality level of 'probable or highly probable', and 22% were assigned a causality level of 'possible'. Two-thirds of the animals in incidents were dogs, and the remaining one-third were cats. Most minor, moderate, and major cases were considered to be causally-related to the applied product; all of these incidents occurred in Canada. Most deaths were considered unrelated to product use. Often, there was either insufficient information contained in the incident report to assess a causality level for cases where the animal died, or the death was considered unlikely related to product use based on the exposure information provided in the report or on the available scientific information for the pesticide. Most causally-related deaths were assessed as 'possible' only, as several factors could have contributed to the deaths, and details in all reports were limited. Almost all deaths reported were from the United States, with only 24 of the causally-related deaths occurring in Canada, comprising 0.4% of all incidents included in the analysis.

Reported Effects

In the incident reports, cats and dogs generally displayed a similar spectrum of effects following application of a spot-on product. In Canadian and American causally-related spot-on incidents, 54% of the animals displayed signs of being uncomfortable or not feeling well. Reported signs included behavioural, gastrointestinal and systemic effects such as lethargy, hyperactivity, abnormal behaviour, vocalization, anorexia, emesis and hypersalivation. Skin effects were common (seen in 57% of all causally-related cases). In nearly 40% of the animals with skin effects, medical treatment was provided. The signs described in animals included pruritus, dermatitis/eczema, and lesions. Neurological effects (22% of causally-related incidents) were frequently observed in the more serious cases; approximately 40% of animals classified as moderate or higher severity experienced signs like muscle tremors, paraesthesia, ataxia or convulsions. Death following the use of a spot-on product occurred in 8% of the causally-related incidents (7.6% were American incidents, while only 0.4% occurred in Canada). Other serious effects, such as neurological signs, often preceded death.

Variables of the Analysis

To determine possible mitigation measures, a number of variables from the incident report data were considered for incidents in which the product was used according to label directions. These variables included the active ingredient(s) contained in the product, animal age and body weight, dose applied, and product point of sale. This analysis relied primarily on Canadian incident reports; however, American incident reports were used as supporting evidence. The analysis

considered only causally-related incidents where the animal was directly exposed to the product and the product was reported to have been used according to label directions.

1. Active Ingredient-Specific Results of the Analysis of Animal Incident Reports

a. Permethrin

Sixty-five percent of dog incidents involved a product containing permethrin, despite the fact that the sales of these products comprise only 30% of all spot-on product sales. Spot-on products with permethrin are typically co-formulated with other active ingredients, including (S)-Methoprene, imidacloprid or pyriproxyfen. However, based on the toxicological profile of the active ingredients, as well as the fact that the concentration of permethrin in spot-on products is higher (generally 45%) than that of the other active ingredients (generally less than 10%) the effects in these incidents were consistent with, and therefore considered to be largely attributed to, permethrin. More than half of treated dogs experienced what are considered to be minimally bothersome skin effects (predominantly pruritus). In some cases involving skin effects, medical treatment was provided. In one-third of the incidents, dogs exhibited behavioural effects (particularly hyperactivity). Dogs that weighed 11 kg or less were twice as likely to experience adverse effects when compared to large (>11 kg) dogs when the incidents were normalized for the number of spot-on units sold however, the severity of incidents was unaffected by dog weight. The data suggest that the applied dose and toxicity of permethrin, along with the body weight of the animal treated, are the main factors contributing to the number of incidents involving permethrin.

b. (s)-Methoprene

Spot-on products containing (S)-Methoprene are registered for use on cats and dogs. For dogs, most products are co-formulated with permethrin. As it was determined that permethrin was the main contributing factor in the dog incidents, the review of (S)-Methoprene focused on cat incidents. (S)-Methoprene-containing products used on cats make up 18% of the spot-on incidents and 16% of the spot-on products sold.

Products containing (S)-Methoprene accounted for 75% of the cat incidents considered in the analysis. A larger number of smaller and younger (<1 year old) cats were affected in incidents with (S)-Methoprene products. The absence of a labelled weight range for products containing (S)-Methoprene means that smaller cats receive a higher dose of product on a mg/kg body weight (mg/kg bw) basis than larger cats. Regardless of age or weight of the animal, approximately 70% of all (S)-Methoprene cat incidents were minor in nature. The adverse effects most frequently reported in cats included drooling, hair loss, and behavioural changes. In some incidents, more severe skin signs that required medical treatment, such as dermatitis or lesions, were reported as well as more serious neuromuscular effects such as ataxia and convulsions. In addition, there were a few instances where cats died following treatment. (S)-Methoprene was not likely to have been a significant contributor to the adverse effects reported in cats, based on its toxicity profile. However, the formulants (present at up to 97%) in (S)-Methoprene products may have contributed to the reported effects.

c. Pyriproxyfen

Pyriproxyfen is registered for use on cats or dogs, and is formulated in spot-on products either alone or with permethrin and/or imidacloprid. Most of the incidents involving pyriproxyfen were attributed to the effects of permethrin when these actives were co-formulated in products. It must be noted that very few incidents were received for products that contain either pyriproxyfen alone (27 cats affected) or pyriproxyfen and imidacloprid (47 dogs affected). These products each made up 1% of all spot-on incidents and 5% of all spot-on product sales. There was a lack of consistency between the reported effects and the toxicity profile of pyriproxyfen.

d. Imidacloprid

Spot-on products containing imidacloprid are registered for use on cats and dogs. In some products, imidacloprid is formulated with other active ingredients (pyriproxifen for cats and permethrin and/or pyriproxyfen for dogs). Products containing imidacloprid, excluding those that contain permethrin, make up 16% of all spot-on incidents and 37% of all spot-on sales in Canada. Most incidents reported were minor or moderate in severity. The majority of affected dogs and cats experienced dermal effects. Even in moderate cases, which accounted for almost half of the incidents for imidacloprid-containing products, the most frequently reported effects involved the skin. Systemic, digestive, behavioural, and neurological effects were also reported, although less frequently. Dermal, systemic, digestive, and neurological effects were similar to those observed in the imidacloprid toxicology studies; however, the neurological effects reported in the incidents appeared to be more strongly correlated with a formulant contained in the imidacloprid spot-on products. Overall, cats and dogs experienced mostly transient skin, behavioural, and systemic effects.

e. d-Phenothrin

Spot-on products containing d-phenothrin have been registered since 2013. The Canadian products considered in this analysis contain d-phenothrin alone. Additional products co-formulated with the active ingredient s-Methoprene were registered in 2018, but were not considered as part of this review. Reporting for products containing d-phenothrin is low, averaging approximately 10 incidents per year since the time of registration; therefore the ability to draw any conclusions from the data was limited. Almost half of the Canadian incidents were submitted to the PMRA prior to product registration, and involved the misuse of a dog product purchased in the United States and used on a cat. Following product registration, reports of this type of misuse decreased and most incidents were minor or moderate in nature. Skin, neurological, and gastrointestinal effects were the most commonly reported signs in dogs. The observed effects were similar to those observed in d-phenothrin toxicology studies. Overall, following product registration, the number of reports of misuse on cats decreased in Canada and the incident reports in dogs indicated mostly transient health effects.

2. Animal Age and Weight

The ages of dogs and cats in reported incidents were compared to the demographics of the cat and dog population in Canada.[9] The mean age of cats in reported spot-on incidents was 4.7 years, whereas the mean age of cats in the general Canadian population is 5.7 years. There was a higher proportion of young cats in the spot-on incident data when compared to the proportion that this demographic represents in the general cat population; 16% of the cat incidents involved animals that were less than 1 year of age versus 8% in the general population. When analyzed by active ingredient, the same pattern emerged for (S)-Methoprene, whereas the age breakdown for cats treated with other active ingredients reflected the general cat population demographics. Thirty-seven percent of the affected cats in the spot-on incident data weighed 4 kg or less; for (S)-Methoprene-related incidents, 70% of cats weighed 4 kg or less. It should be noted that spot-on products containing (S)-Methoprene are not weight-banded. Although younger, smaller cats appear to be more sensitive to products that contain (S)-Methoprene, there was no notable difference in the severity of the effects reported.

The mean age (4.8 years) of dogs in reported spot-on incidents was also slightly lower than the mean age (5.8 years) of dogs in the general Canadian population. Dogs 3 years of age or younger were only slightly more represented in the incident data when compared to the same age range in the Canadian dog population (41% versus 36%). Although there was a slight indication that younger dogs are more frequently reported in incidents, overall, age did not seem to be a major contributor in dog incidents. Fifty-nine percent of dogs in spot-on incidents weighed less than 11 kg, whereas dog spot-on products with a similar weight band constitute 40% of sales. This resulted in an incident rate for dogs weighing less than 11 kg that is double that for dogs weighing more than 11 kg. This higher rate of incidents in smaller dogs was seen for all the spot-on active ingredients, but was most notable for products containing permethrin, as they accounted for the highest volume of incident reports involving dogs.

The analysis of age and weight indicates that these variables were not the main determining factors in the incidents reported, although some patterns emerged for each variable for specific active ingredients and/or products.

3. Applied Dose

As spot-on products are pre-packaged, sometimes with weight bands, the dose applied to the animal based on its body weight can vary. A high degree of variability in the applied doses and small sample sizes in certain cases limited the analysis of applied dose with respect to severity of incident, number of animals affected, and incident rate. Despite these limitations, general observations were made.

In general, both the average dose and the range of dose of spot-on product applied to cats were higher than for dogs. These observations are likely due to the fact that many cat spot-on products do not have weight band restrictions.

---

9 Perrin, T. "The Business of Urban Animal Survey: The fact and statistics on companion animals in Canada.," Can Vet J. 2009 Jan; 50(1): 48-52.

Based on the analysis, the doses of permethrin and d-phenothrin applied to dogs (in mg/kg bw) are relatively high compared to the other active ingredients in spot-on products, due to the higher percentage content of permethrin (as high as 45%) and phenothrin (as high as 86%) versus other active ingredients in spot-on products (0.4–9%). The applied doses for several formulants contained within spot-on products are also relatively high, particularly for cat products, due to their high percentage content in the products (in some cases over 90%). However, overall, there were no strong associations between applied dose (in mg/kg bw) and the incident severity or rate when normalized for product sales.

4. Point of Sale

In Canada, manufacturers sell spot-on products either through veterinary clinics or in retail stores.

Incidents were reported slightly more often for products available exclusively through veterinary clinics; however, this was directly proportional to product sales, indicating that the location of sale (veterinary clinic or retail store) has no bearing on the rate of incidents reported.

Prior to the implementation of mitigation measures outlined in DIR2010-02, the location of sale had an impact on the number of cases of misuse. More cases of misuse involving products purchased at a retail outlet were reported at that time. Following the mitigation measures outlined in DIR2010-02, no notable differences were observed between points of sale.

3.0 Animal Safety Testing Strategies

As part of its pre-market assessment of pesticide products used on companion animals, the PMRA requires data to assess the safety to treated animals. Similar requirements are in place for veterinary drug products regulated by the Veterinary Drugs Directorate (VDD) of Health Canada's Health Products and Food Branch for use on companion animals. A product applied dermally to an animal for the exclusive control of ectoparasites (pests that live on the outside of an animal) is classified as a pesticide, and is thus regulated by the PMRA.

A product is classified as a drug if it is intended to control endoparasites (pests that live inside an animal) regardless of method of application, and ectoparasites if administered other than by topical application; such products are regulated by the VDD.[10]

---

10 "DIR 94-07 Products Subject to the Pest Control Products Act and the Food and Drugs Act." Health Canada, Pest Management Regulatory Agency. July 13, 1994.

For pesticide products, the CAS study[11] is the core study used to assess animal safety. A similar study, the margin of safety study, is required for veterinary drugs[12 13]. The design of the CAS and margin of safety studies are similar in that groups of animals representing the target population are treated with the pesticide or drug at the intended label dose as well as at exaggerated doses which are typically three-times and five-times the intended label dose. The animals are then assessed for potential adverse effects. These studies are performed in a laboratory on healthy animals that represent a fairly homogeneous population. Typically, test groups consist of four to six animals per sex per dose level.

As a result of the current analysis of incident reports, it was determined that the CAS studies available for the spot-on pesticide products were of limited value as a predictive tool, particularly in detecting less common findings that may become evident only following wide-scale use in many animals.

For veterinary drugs, in addition to the margin of safety study, a clinical safety study is required. The clinical safety study provides an evaluation of potential adverse effects at the intended label dose under actual use conditions and often is designed to include an assessment of the efficacy of a proposed drug. When compared to the CAS study, the clinical safety study involves a larger group size, increasing the chance of detecting adverse reactions, as well as a more diverse test group representative of the target population. A clinical safety study is not currently required by the PMRA to assess the safety of a pesticide product used on companion animals.

The results of this analysis highlight the need to improve the current animal safety testing strategy for pesticide products used on companion animals.

4.0 Other Available Information

The PMRA also consulted the Canadian Veterinary Medical Association National Issues Committee. Canadian Veterinary Medical Association members provided input on risk acceptability, possible mitigation options to decrease the number of incident reports for spot-on products, and improvements to testing strategies. Some members indicated that treatment of minor signs is a common practice to soothe the pet or owner, and that therefore many of the cases classified as moderate by the PMRA were actually minor in nature. Members agreed that labelling would help to inform consumers which signs are minor and expected, and also inform consumers that they should contact their veterinarian or the registrant when signs are observed. They felt that testing strategies for spot-on products should align with Health Canada's VDD.

---

11 "Health Effects Test Guidelines: OPPTS 870.7200 Companion Animal Safety [EPA 712–C–98–349]." Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency. August 1998.

12 "Guidance for Industry Preparation of Veterinary New Drug submissions. Health Canada Veterinary Drugs Directorate." March 2007.

13 "Target Animal Safety for Pharmaceuticals VICH GL43." Veterinary International Co-operation on Harmonization (of Technical Requirements for Registration of Veterinary Medicinal products – EU). July, 2008.

Discussions with permethrin registrants and a representative from Safety Call International, a company that manages adverse events for animal health products, also took place. Some registrants provided information on clinical safety trials conducted in other jurisdictions that show that some minor signs are expected with the use of spot-on products. Registrants felt that labelling of the most commonly occurring adverse effects would be a positive step towards informing consumers and better aligning with veterinary drugs used to treat fleas and ticks.

The PMRA also considered the regulatory approach to spot-on products in other jurisdictions. In several regulatory jurisdictions, adverse effects observed in animal safety studies and in post-market pharmacovigilance data are reflected in the caution, precaution, and/or contraindication statements on the product label. The labelling of adverse effects allows the veterinarian and/or pet owner to make an informed decision regarding product use when considering its benefits to the animal. The USEPA has required the listing of side effects on the product label since their 2009 review of spot-on incidents. As mentioned above, Health Canada's VDD requires clinical safety studies under field use conditions. The adverse effects listed on product labels are derived from these studies. Many of the spot-on products registered at the PMRA are registered as veterinary drugs at the European Union Veterinary Medicines Branch of the European Medicines Agency. As such, the data requirements and labelling of adverse effects is similar to the process at Health Canada's VDD.

5.0 Conclusion

The PMRA analyzed 5928 animal incident reports involving spot-on products. Most Canadian incidents were considered to be associated with appropriate product use and not to other, extraneous factors. Minor and moderate incidents made up the majority of the database. The results of the analysis indicated that many of the variables considered (such as animal age and body weight, applied dose, and point of sale) were not important factors in the number or the severity of incidents received. In some cases, however, patterns of involvement with these variables were noted for specific active ingredients and/or products. Regardless of specific patterns observed in the analysis, the spectrum of observed effects was generally the same across the spot-on incidents and predominantly involved minor skin, gastrointestinal, and behavioural effects.

Despite the high number of incident reports received for spot-on products, the PMRA recognizes the value that these products have in the marketplace in protecting cats and dogs from potential infection and disease. Consideration was given to the severity of the effects observed in the reported incidents (which were predominantly minor to moderate) in relation to the seriousness of the conditions that may result from contact with pests (such as fleas and ticks).

5.1 Proposed Label Requirement

As a measure to better inform the consumer as to the possible effects that may be expected following product use, the PMRA is requiring registrants and applicants of spot-on products to list potential side effects on the product label. This proposed requirement aligns with practices already in place for drugs and companion animal products in other areas of Health Canada and in other jurisdictions such as the United States and Europe.

For currently registered spot-on products, as well as those under evaluation by the PMRA, the registrant must place a box on the product label under the precautions section titled 'Side Effects'. Registrants must use the language below or propose their own side effects language based on incident reports, companion animal safety studies, and/or clinical trials, if available.

For products used on dogs:

Monitor your dog after application. Side effects may include: skin irritation such as redness or scratching; changes in behaviour such as agitation or lethargy; or gastrointestinal effects such as vomiting or loss of appetite. If these or other side effects occur consult your veterinarian or [Registrant at 1-800-number].

For products used on cats:

Monitor your cat after application. Side effects may include: skin irritation such as scratching or hair loss at the application site, or changes in behaviour such as agitation or lethargy. Gastrointestinal effects such as drooling, vomiting, or loss of appetite may also occur. If these or other side effects occur, consult your veterinarian or [Registrant at 1-800-number].

The review also highlighted the lack of consistency in the use directions on product labels; therefore, the following label improvements are required on all spot-on product labels.

- Remove label language that allows re-application of the product before the end of the effective control period. For example, products that are labelled as providing four weeks of control may also have statements such as "Reapply after one week if necessary".

- Add label language to contraindicate use of other flea control products with the same active ingredients as the spot-on (for example, "This product contains [*name of active ingredient(s)*]. Do not apply another pest control product such as a shampoo, collar, or powder which contains [*name of active ingredient(s)*] to the treated animal when using [*name of spot-on product*]").

5.2 Proposed Data Requirement

The results of this analysis highlight the need to strengthen the current data requirements for animal safety testing for pesticide products used on companion animals. The PMRA is therefore proposing that the data requirements for pesticide products for use on companion animals under

Use-Site Category 24 be amended to include a clinical safety study in addition to a CAS study (DACO 4.6.9). Clinical safety data obtained under actual use conditions will enhance the PMRA's pre-market assessment of the safety of these products. Data obtained from a clinical safety study will provide the PMRA with more extensive information with which to assess the safety of these products, and subsequently communicate key information on the product label relating to possible adverse effects. Moreover, this proposed amendment to the data requirements allows the PMRA to be more closely aligned with Health Canada VDD's approach for regulating similar products.

Following the final decision on this proposal, any subsequent submissions to register a product for use on companion animals will be required to submit the above-mentioned clinical safety data. The PMRA recommends that applicants consult the guidelines and guidance issued by the VDD and the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products when designing clinical safety studies. Applicants are also encouraged to undertake a pre-submission consultation with the PMRA for specific recommendations on proposed study protocols prior to study conduct. These studies can be designed to assess concomitantly the efficacy of the proposed product under actual conditions of use.

6.0 Next Steps

The PMRA invites the public to submit written comments on this proposal up to 45 days from publication. The PMRA will consider all comments received before making a final decision. Please note that submitted comments should be limited to those relating to the proposed label requirements and data requirements discussed in this proposal. Comments are not being solicited on the analysis of spot-on incidents. Please forward all comments to Publications.

Please provide your comments and include the following information: your full name and organization, telephone number, and complete mailing address or e-mail address.

Any inquiries should be directed to the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (hc.pmra.info-arla.sc@canada.ca).